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The efficacy of irinotecan supplementation for colorectal cancer

A meta-analysis of randomized controlled studies

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Abstract

Background: The efficacy of irinotecan as the adjunctive therapy to fluorouracil and leucovorin remains controversial in patients with colorectal cancer. We conduct this meta-analysis to explore the efficacy of irinotecan supplementation for colorectal cancer.

Methods: We have searched PubMed, EMBASE, Web of science, EBSCO, and Cochrane library databases through March 19, 2020, and included randomized controlled trials assessing the efficacy of irinotecan plus fluorouracil and leucovorin for colorectal cancer.

Results: Five randomized controlled trials were included in the meta-analysis. Compared with fluorouracil and leucovorin for colorectal cancer, irinotecan supplementation could significantly improve progression-free survival rate (hazard ratio = 0.72; 95% confidence interval [CI] = 0.58–0.90; P = .003), median progression-free survival (standard mean difference = –0.30; 95% CI = –0.44 to –0.15; P < .0001), overall survival rate (hazard ratio = 0.77; 95% CI = 0.66–0.90; P = .001), and objective response (risk ratio [RR] = 0.57; 95% CI = 0.49–0.66; P < .00001) and decrease progressive disease (RR = 2.10; 95% CI = 1.40–3.14; P = .0003), but revealed no obvious effect on complete response (RR = 0.88; 95% CI = 0.33–2.29; P = .79). The incidence of grade ≥3 adverse events in irinotecan supplementation group was increased compared to control group (RR = 0.67; 95% CI = 0.57–0.79; P < .00001).

Conclusions: Irinotecan as the adjunctive therapy to fluorouracil and leucovorin can increase the survival and objective response of patients with colorectal cancer, but the incidence of grade ≥3 adverse events is found to be increased after irinotecan supplementation.

Abbreviations: CI = confidence interval, HR = hazard ratio, RCT = randomized controlled trials, RR = risk ratio.

Keywords: colorectal cancer, fluorouracil, irinotecan, leucovorin, randomized controlled trials

1. Introduction

Colorectal cancer is regarded as a significant cause of mortality.[1–3] The prognosis of these patients is determined by the stages of colorectal cancer, and 5-year survival rates of stage I, II, and III after surgical intervention are 93.2%, 82.5%, and 59.5%, respectively. Especially, 5-year survival rate of stage IV is only 8.1%.[4] Many patients with resected cancer may suffer from recurrence.[5,6] Fluorouracil and leucovorin have been widely used for colorectal cancer,[7] and are reported to reduce the recurrence rate and improve survival.[8]

In order to improve the treatment efficacy, irinotecan or oxaliplatin is used combined with fluorouracil and leucovorin, and these combinations are generally regarded as the effective approach for advanced colorectal cancer.[9,10] In elderly patients, irinotecan or oxaliplatin in combination with fluorouracil is well tolerated and shows similar efficacy between elderly and younger patients.[11] In metastatic colorectal cancer, combining irinotecan with fluorouracil results in a remarkable increase in progression-free survival and overall survival than fluorouracil alone.[12]

However, current evidence is insufficient for routine use of irinotecan supplementation for colorectal cancer, and several studies have reported the conflicting results of irinotecan supplementation for colorectal cancer.[4,9,13,14] This meta-analysis aims to assess the efficacy and safety of irinotecan in combination with fluorouracil and leucovorin for colorectal cancer.

2. Materials and methods

This meta-analysis was performed based on the Preferred Reporting Items for Systematic Reviews and Meta-analysis statement and Cochrane Handbook for Systematic Reviews of Interventions.[15,16] No ethical approval and patient consent were required because all analyses were based on previously published studies.

The authors have no funding and conflicts of interest to disclose.

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

Compliance with ethical standards.

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2.1. Literature search

We have systematically searched several databases including PubMed, EMBASE, Web of science, EBSCO, and the Cochrane library from inception to March 19, 2020 with the following keywords: "irinotecan" AND "fluorouracil" AND "leucovorin" AND "colorectal cancer" OR "colon cancer" OR "rectal cancer".

The inclusion criteria were as follows: study design was RCT, patients were diagnosed with colorectal cancer, and intervention treatments were irinotecan plus fluorouracil and leucovorin versus only fluorouracil and leucovorin. Patients who previously received pelvic radiotherapy were excluded.

2.2. Data extraction and outcome measures

Some baseline information was extracted, and they included first author, number of patients, age, sex, performance status, primary tumor site (colon/ rectum/both), and detail methods in 2 groups. Data were extracted independently by 2 investigators, and discrepancies were resolved by consensus. The primary outcomes were progression-free survival rate, median progression-free survival, and overall survival rate. Secondary outcomes included objective response, progressive disease, complete response, and grade ≥3 adverse events.

2.3. Assessment for risk of bias

The risk of bias tool was used to assess the quality of individual studies according to the *Cochrane Handbook for Systematic Reviews of Interventions*,[16] and the sources of bias were divided into selection bias, performance bias, attrition bias, detection bias, reporting bias, and other potential sources of bias. The overall risk of bias for each study was evaluated and rated: low, unclear, and high.[17] Two investigators independently assessed the quality of included studies, and any discrepancy was solved by consensus.

2.4. Statistical analysis

We assessed hazard ratio (HR) or risk ratio (RR) with 95% confidence interval (CI) for dichotomous outcomes (progression-free survival rate, overall survival rate, objective response, progressive disease, complete response, and grade ≥3 adverse events) and standard mean difference with 95% CI for continuous outcome (median progression-free survival). Heterogeneity was evaluated by the I^2 statistic, and $I^2 > 50\%$ indicated significant heterogeneity.[18] The random-effects model was used when encountering significant heterogeneity, while fixed-effects model was applied when no significant heterogeneity was found. We searched for potential sources of heterogeneity, and sensitivity analysis was performed to detect the influence of a single study on the overall estimate via omitting 1 study in turn or conducting the subgroup analysis. Owing to the limited number (<10) of included studies, publication bias was not assessed. A P value of <.05 was indicated to be statistically significant. All statistical analyses were performed using Review Manager Version 5.3 (The Cochrane Collaboration, Software Update, Oxford, United Kingdom).

3. Results

3.1. Literature search, study characteristics, and quality assessment

Figure 1 shows the detail flowchart of the search and selection results. Five hundred ninety-eight potentially relevant articles were initially identified. Two hundred twenty-three duplicates and 366 papers after checking the titles/abstracts were excluded. Four studies were removed because of different combination drugs, and 5 randomized controlled trials (RCTs) were finally included in the meta-analysis.[4,9,13,14,19]

The baseline characteristics of 5 included RCTs are shown in Table 1. These studies were published between 2000 and 2015, and the total sample size was 4536. All included RCTs reported irinotecan as the adjunctive therapy to fluorouracil and leucovorin, and the methods between irinotecan group and control group were different in each RCT, detailed in Table 1. In the study by Saltz,[14] we just extracted the data of study 2 (Douillard) for this meta-analysis in order to avoid the duplicated data of Saltz.[19]

Four studies reported progression-free survival rate,[4,9,13,19] 2 studies reported median progression-free survival,[9,13] 4 studies reported overall survival rate and objective response,[9,13,14,19] 2 studies reported progressive disease and complete response,[9,13] and 3 studies reported grade ≥3 adverse events.[9,13,19]

3.2. Assessment of risk of bias

Risk of bias analysis is presented in Figure 2. These 5 included RCTs generally had high quality although 4 studies had high risk of bias due to their nonblindness.[4,9,14,19]

3.3. Primary outcomes: progression-free survival rate, median progression-free survival, and overall survival rate

Compared to control group for colorectal cancer, irinotecan supplementation was associated with substantially improved progression-free survival rate (HR = 0.72; 95% CI = 0.58–0.90; P = .003) with significant heterogeneity among the studies (I^2 = 88%, heterogeneity P < .0001; Fig. 3), median progression-free survival (standard mean difference = –0.30; 95% CI = –0.44 to –0.15; P < .0001) with no heterogeneity among the studies (I^2 = 0%, heterogeneity P = .79; Fig. 4), and overall survival rate (HR = 0.77; 95% CI = 0.66–0.90; P = .001) with no heterogeneity among the studies (I^2 = 0%, heterogeneity P = .98; Fig. 5).

3.4. Sensitivity analysis

There was significant heterogeneity for progression-free survival rate, but no heterogeneity was observed for median progression-free survival or overall survival rate. As shown in Figure 3, the study conducted by Van Cutsem et al[4] showed the results that were almost completely out of range of the others and probably contributed to the heterogeneity. After excluding that study, the results suggested that irinotecan supplementation could also improve progression-free survival rate for colorectal cancer than control intervention (HR = 0.65; 95% CI = 0.63–0.67; P < .00001). No evidence of heterogeneity was observed among the remaining studies (I^2 = 0%).

3.5. Secondary outcomes

In comparison with control group for colorectal cancer, irinotecan supplementation showed the obvious increase in objective response (RR = 0.57; 95% CI = 0.49–0.66; P < .00001; Fig. 6) and the decrease in progressive disease (RR = 2.10; 95% CI = 1.40–3.14; P = .0003; Fig. 7), but had no substantial impact on complete response (RR = 0.89; 95% CI = 0.37–2.13; P = .79; Fig. 8). In addition, the incidence of grade ≥3 adverse events in irinotecan supplementation group was higher than that in control group (RR = 0.67; 95% CI = 0.57–0.79; P < .00001; Fig. 9).

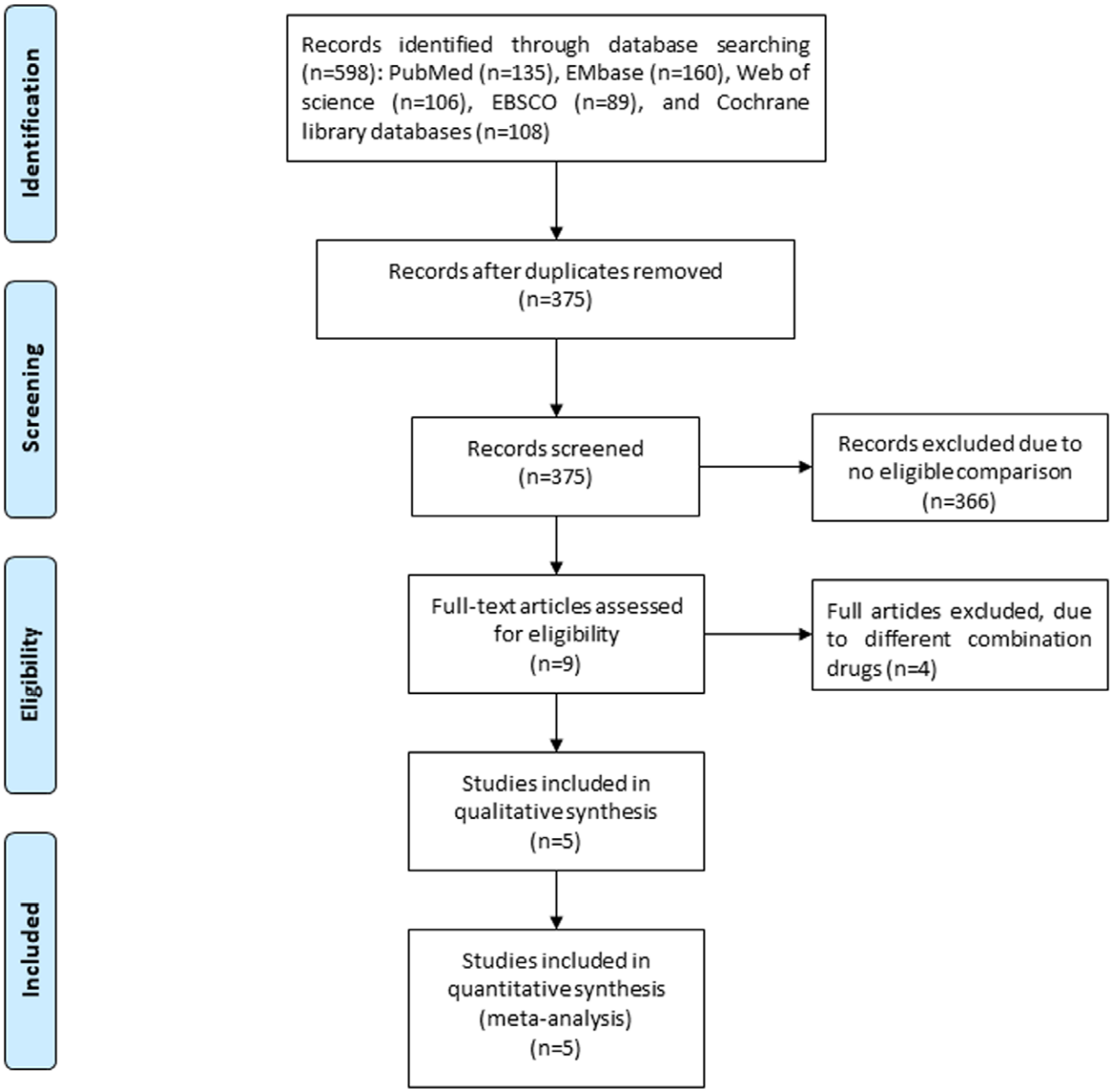

Figure 1. Flow diagram of study searching and selection process.

4. Discussion

Irinotecan was documented to be an effective topoisomerase I inhibitor with antitumor properties and its combination with fluorouracil/leucovorin was found to improve the outcomes of patients with metastatic colorectal cancer.[20,21] In contrast, in another trial involving patients with stage III colon cancer, irinotecan plus fluorouracil/leucovorin did not improve overall survival compared with fluorouracil/leucovorin alone.[4] Considering these inconsistence, our meta-analysis was performed and confirmed that irinotecan in combination with fluorouracil and leucovorin could substantially improve progression-free survival rate, median progression-free survival, overall survival rate, and objective response and reduce the incidence of progressive disease for colorectal cancer compared to only fluorouracil and leucovorin, but revealed no obvious influence on complete response.

Regarding the sensitivity analysis, significant heterogeneity remains for progression-free survival rate. Three studies reported metastatic colorectal cancer,[9,13,19] while the remaining study conducted by Van Cutsem et al[4] reported colon cancer with stage III. After excluding that study, there was no heterogeneity found. Irinotecan supplementation can also improve progression-free survival rate for colorectal cancer ($P < .00001$) than control intervention. These indicated that irinotecan plus fluorouracil and leucovorin may have better efficacy to improve progression-free survival rate in stage IV colorectal cancer than that in stage III colorectal cancer.

In addition, patient populations with different age ranges may have some impact on the efficacy of irinotecan supplementation. For instance, adding irinotecan to fluorouracil for metastatic colorectal cancer showed no significant impact on progression-free survival in patients aged ≥75.[13] In contrast, a post hoc analysis demonstrated that irinotecan plus fluorouracil can improve progression-free survival than fluorouracil alone in patients only aged 70 to 75 years, but this efficacy was not observed in patients aged >75 years.[13]

Table 1

Characteristics of included studies.

		Irinotecan group						Control group					
No.	Author and year	Number	Age, median (range)	Female (n)	Performance status 0/1/2 (n)	Primary tumor site, colon/ rectum/ both (n)	Methods	Number	Age, median (range)	Female (n)	Performance status 0/1/2 (n)	Primary tumor site, colon/ rectum/ both (n)	Methods
1	Aparicio, 2015[13]	71	80.1 (74.7–90.3)	25	–	56/12/2	Leucovorin 200 mg/m^2 as a 2-h IV infusion, fluorouracil 400 mg/m^2 IV bolus, and fluorouracil 600 mg/m^2 as a 22-h CI at day 1 and day 2 every 2 wk plus irinotecan at day 1 as a 90-min IV perfusion 150 mg/m^2 and then 180 mg/m^2 after the second cycle	70	79.9 (75.1–91.3)	34	–	54/14/1	Leucovorin 200 mg/m^2 as a 2-h IV infusion, fluorouracil 400 mg/m^2 IV bolus, and fluorouracil 600 mg/m^2 as a 22-h CI on day 1 and day 2 every 2 wk
2	Van Cutsem, 2009[4]	1497	60 (21–76)	663	1222/272/0	–	Leucovorin 200 mg/m^2 as a 2-h infusion, followed by fluorouracil as a 400 mg/m^2 bolus and then a 600 mg/m^2 CI over 22 h, days 1 and 2, every 2 wk for 12 cycles plus irinotecan (180 mg/m^2 as a 30- to 90-min infusion, day 1, every 2 wk)	1485	60 (18–76)	659	1228/250/0	–	Leucovorin 200 mg/m^2 as a 2-h infusion, followed by fluorouracil as a 400 mg/m^2 bolus and then a 600 mg/m^2 CI over 22 h, days 1 and 2, every 2 wk for 12 cycles
3	Köhne, 2005[9]	216	60.5 (24–80), median (range)	84	126/81/9	101/114/1	Leucovorin 500 mg/m^2 as a 2-h infusion and fluorouracil 2.3 or 2.0 g/m^2 by IV 24-h infusion, both administered weekly for 6 wk plus irinotecan 80 mg/m^2 administered over 30 min	214	61 (32–78)	78	120/84/10	118/96/0	Leucovorin 500 mg/m^2 as a 2-h infusion and fluorouracil 2.6 g/m^2 by IV 24-h infusion, both administered weekly for 6 wk, followed by a 2-wk rest
4	Saltz, 2001[14]	187	59 (24–75), median (range)	88	95/77/15	121/66	Fluorouracil (2.3 g/m^2/wk × 6 wk, q 7 wk) and leucovorin (500 mg/m^2/wk × 6 wk, q 7 wk) plus irinotecan (80 mg/m^2/wk × 6 wk, q 7 wk) or fluorouracil (400 IV/600 CI mg/m^2 day 1, day 2 q 2 wk) and leucovorin (200 mg/m^2 day 1, day 2 q 2 wk) plus irinotecan (180 mg/m^2 day 1 q 2 wk)	198	62 (27–75)	65	101/83/14	109/89	Fluorouracil (2.6 g/m^2/wk × 6 wk, q 7 wk) and leucovorin (500 mg/m^2/wk × 6 wk, q 7 wk) or fluorouracil (400 IV/600 CI mg/m^2 day 1, day 2 q 2 wk) and leucovorin (200 mg/m^2 day 1, day 2 q 2 wk)
5	Saltz, 2000[19]	226	61 (19–85)	101	93/102/29	192/31/–	Irinotecan (125 mg/m^2 of body surface area IV over a 90-min period), leucovorin (20 mg/m^2 as an IV bolus) and fluorouracil (500 mg/m^2 as an IV bolus), given weekly for 4 wk every 6 wk	231	62 (25–85)	79	89/106/35	188/38/–	Leucovorin (20 mg/m^2 as an IV bolus) and fluorouracil (425 mg/m^2 as an IV bolus), given daily for 5 d (on days 1–5) every 4 wk

CI = continuous infusion, IV = intravenous.

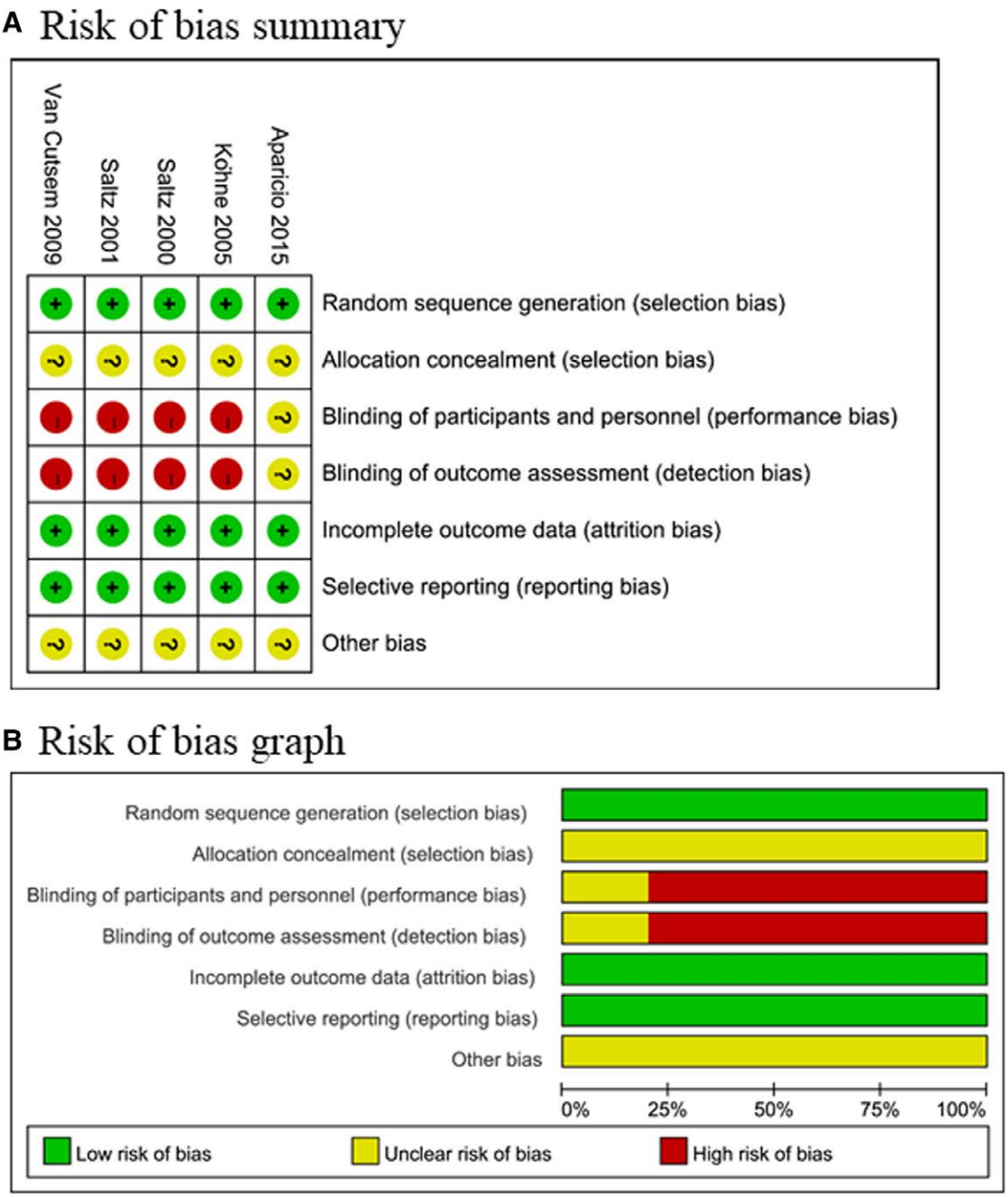

Figure 2. Risk of bias assessment. (A) Authors' judgments about each risk of bias item for each included study. (B) Authors' judgments about each risk of bias item are presented as percentages across all included studies.

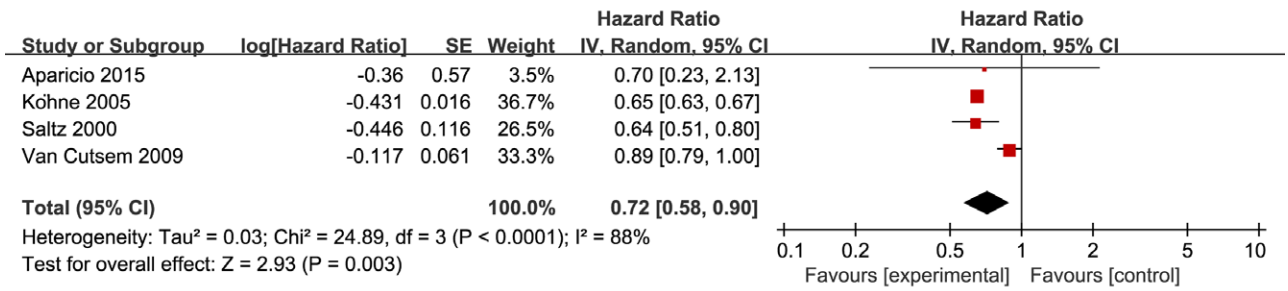

Figure 3. Forest plot for the meta-analysis of progression-free survival rate. CI = confidence interval, IV = intravenous, SE = standard error.

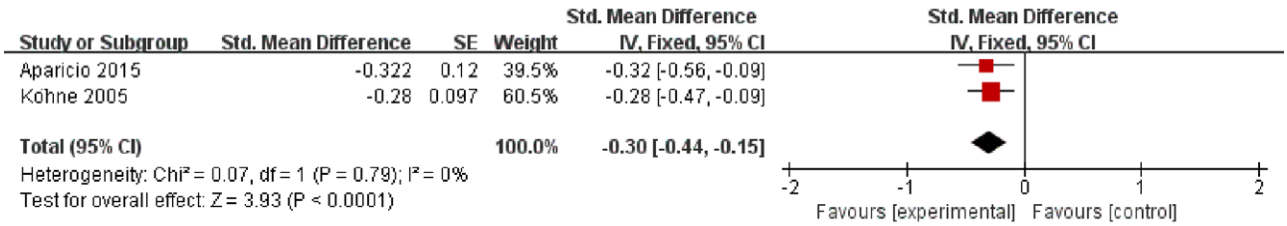

Figure 4. Forest plot for the meta-analysis of median progression-free survival (month). CI = confidence interval, IV = intravenous, SE = standard error.

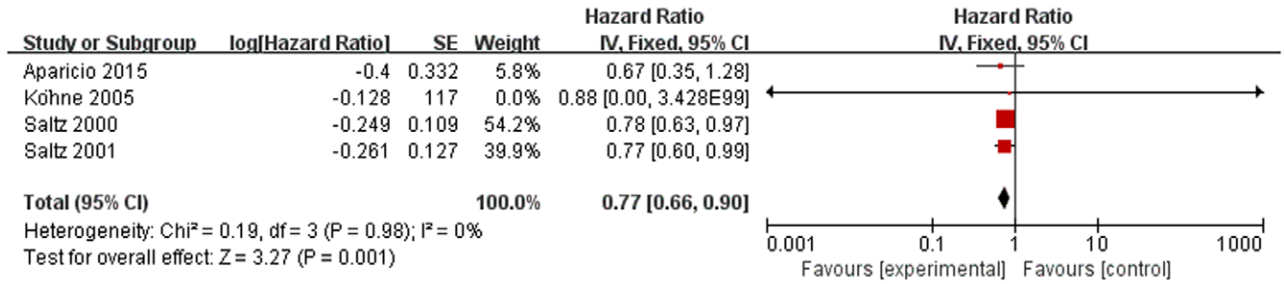

Figure 5. Forest plot for the meta-analysis of overall survival rate. CI = confidence interval, IV = intravenous, SE = standard error.

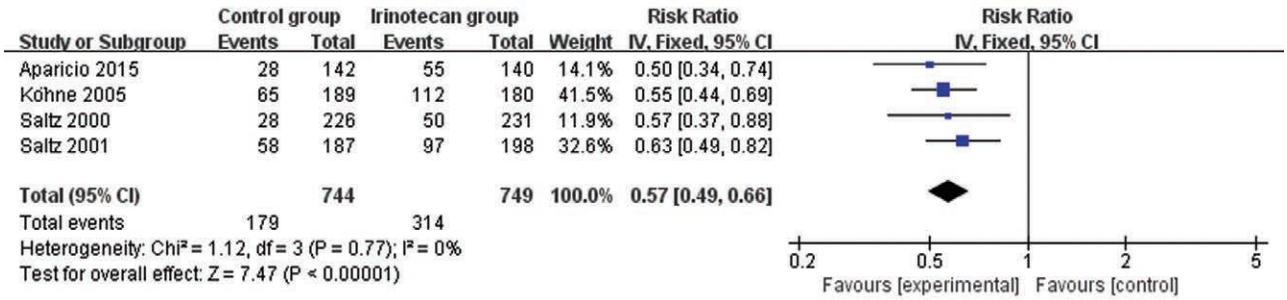

Figure 6. Forest plot for the meta-analysis of objective response. CI = confidence interval, IV = intravenous.

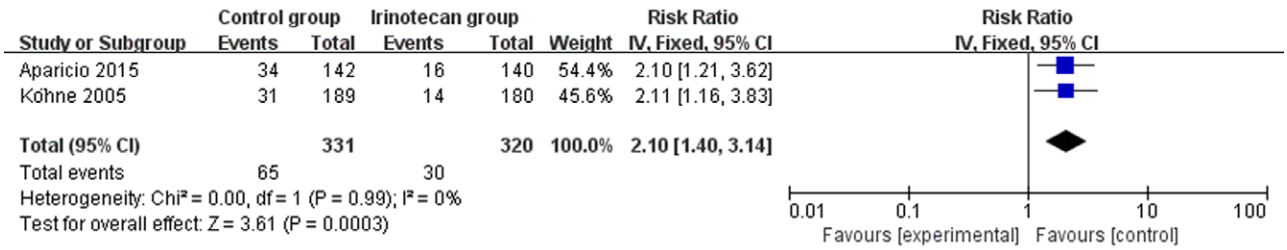

Figure 7. Forest plot for the meta-analysis of progressive disease. CI = confidence interval, IV = intravenous.

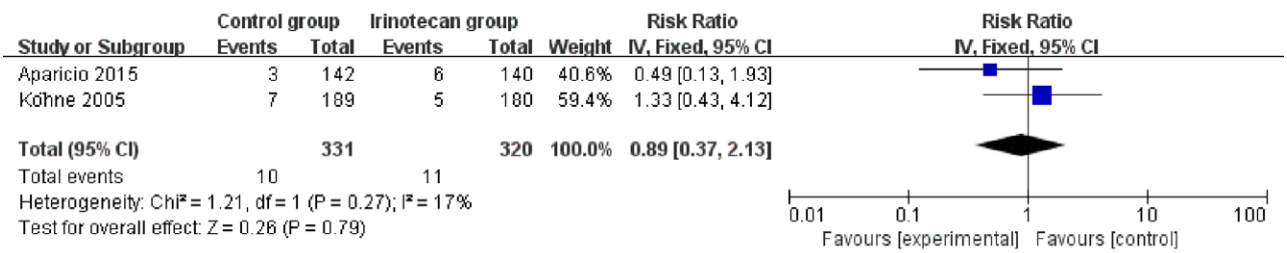

Figure 8. Forest plot for the meta-analysis of complete response. CI = confidence interval, IV = intravenous.

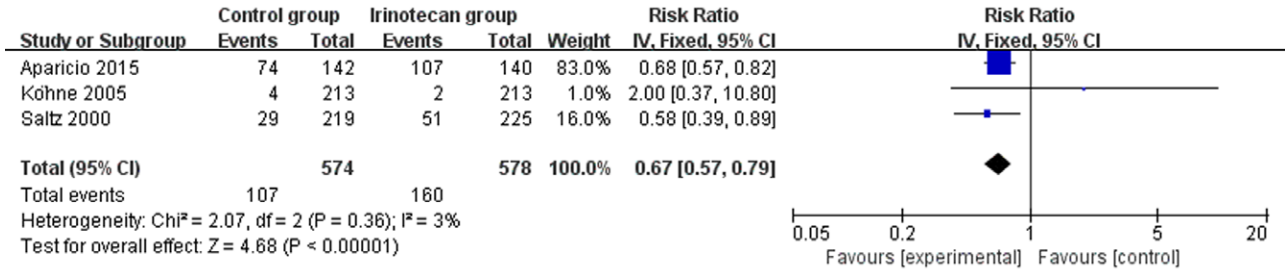

Figure 9. Forest plot for the meta-analysis of grade ≥3 adverse events. CI = confidence interval, IV = intravenous.

Fluorouracil/leucovorin in combination with irinotecan was found to have the advantage of reduced toxicity compared with fluorouracil/leucovorin.[4,13] However, irinotecan supplementation was found to increase the incidence of grade ≥3 adverse events than control group in colorectal cancer based on the results of this meta-analysis. These side effects mainly included diarrhea and neutropenia and were generally manageable and acceptable.[4,9,11,19] Several limitations exist in this meta-analysis. First, our analysis was based on only 5 RCTs, and more RCTs with large sample size should be conducted to explore this issue. Next, there is significant heterogeneity, and these sources of heterogeneity should be assessed by subgroup analysis (different stages of colorectal cancer, patients with various age range, and methods of drug combination). However, it is not possible due to the small number of included studies. Finally, genetic variants such as the expression of metadherin and carcinoembryonic antigen may affect therapeutic response and prognosis of colorectal cancer and produce some bias.[22]

5. Conclusion

Irinotecan supplementation can improve the survival and objective response of colorectal cancer patients receiving fluorouracil and leucovorin, but with the increase in grade ≥3 adverse events.

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